

Bone marrow cell therapy after myocardial infarction. What should we select?

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This editorial refers to ‘Intracoronary infusion of bone marrow-derived selected CD34⁺CXCR4⁺ cells and non-selected mononuclear cells in patients with acute STEMI and reduced left ventricular ejection fraction: results of the randomized, multicentre Myocardial Regeneration by Intracoronary Infusion of Selected Population of Stem Cells in Acute Myocardial Infarction (REGENT) Trial’[†], by M. Tendera *et al.*, on page 1313

The promise of a stem/progenitor cell-mediated cardiac repair after myocardial infarction (MI) has fascinated basic scientists and clinical cardiologists alike, and initial small- and intermediate-scale clinical studies have examined the effects of a single intracoronary administration of unfractionated or mononuclear bone marrow cells (BMCs) on left ventricular (LV) function in patients after MI. Several recent meta-analyses of these controlled clinical studies have suggested a moderate, but significant, improvement of LV ejection fraction (EF) by BMC therapy in patients after MI.^{1,2} The most recent meta-analysis by Martin-Rendon *et al.* reported an improvement in LVEF of 2.99% in patients undergoing BMC therapy after MI.² This was close to the observed improvement in LVEF of 2.5% in the REPAIR-AMI (Remodeling in Acute Myocardial Infarction) trial, the largest randomized, controlled clinical study of BMC therapy in patients after MI.³ Although these potential effects of BMC therapy on LV function are less than many investigators were hoping for, it should be noted that several of our established clinical therapies with an impact on prognosis in patients with MI and a reduced LV function, such as angiotensin-converting enzyme (ACE) inhibitor or β -blocker therapy, are associated with similar improvements in LVEF⁴ and have been observed in patients after MI with a less optimal background therapy as compared with present studies. There are, however, many remaining open questions with respect to mechanisms of stem/progenitor cell therapy after MI and potential strategies to optimize its effects.

To date, BMCs have either been used unfractionated or as mononuclear cells in clinical studies in patients after MI. This clearly

represents a heterogeneous population of cells, so that it remains unclear which of the cells is particularly important for the potential effects on cardiac repair. Tendera *et al.* now report the results of the REGENT trial (Myocardial Regeneration by Intracoronary Infusion of Selected Population of Stem Cells in Acute Myocardial Infarction), a multicentre study comparing the effect of unselected mononuclear BMCs with an ~ 100 times lower number of selected CD34⁺/CXCR4⁺ mononuclear BMCs in patients after MI.⁵ The rationale for selecting CD34⁺/CXCR4⁺ cells was based on the observation from clinical studies that these cells are mobilized from the bone marrow in response to myocardial ischaemia⁶ and from experimental studies indicating that these cells may express endothelial and cardiac lineage markers.⁷

Although 200 patients were randomized to intracoronary infusion of unselected ($n = 80$) or selected ($n = 80$) mononuclear BMCs or to the control group ($n = 40$) without BMC therapy, the primary endpoint of the study was evaluated in 117 patients, i.e. in 58.5% of the patients included in the study. The primary endpoint was defined as change of LVEF and volumes as measured by magnetic resonance imaging (MRI) before and 6 months after the procedure. In the single analysis of each cell therapy group, LVEF increased significantly by $\sim 3\%$, which was not observed in the control group; however, the absolute differences between the groups did not reach statistical significance after Bonferroni correction. A possible explanation for the lack of a significant difference between the groups may be a reduced power of the study, due to the analysis of the primary endpoint in $< 60\%$ of the patients and a smaller change in LVEF after BMC therapy than expected when the study was planned (expected change of LVEF $> 5\%$). This may be supported by the observation that the magnitude of the change of LVEF in the cell therapy groups corresponds well to what has been reported in the above meta-analyses and the largest published randomized study in the field, the REPAIR-AMI trial.³ We have therefore to interpret the results of the REGENT trial with caution, since a limited power of the study may have prevented the authors being able to show a significant difference for the primary endpoint, as has been pointed out by the authors themselves.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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Interestingly, the analysis of potential factors favouring the effect of BMC therapy on LV function in the REGENT trial revealed that a significant increase of LVEF was only observed in patients treated with BMCs who had a baseline LVEF below the median (i.e. LVEF <37%). This corresponds well to the observation in the REPAIR-AMI study that patients with a lower baseline LVEF derived most benefit.³ Therefore, these analyses are generating the hypothesis that selecting patients with a severe impairment of LVEF after MI may be one way to increase the benefit of this therapy.

The study design of Tendera *et al.* did not compare similar numbers of unselected and selected BMCs (the number of selected BMCs was ~100 times lower), and the 'selected' cells remained contained in the unselected BMCs.⁵ Such a selection of subfractions of BMCs would be expected to augment the effect of cell therapy on cardiac function only when there are other cell fractions within BMCs that would exert an inhibitory effect on cardiac repair, which remains largely unknown at present. However, a similar increase of LVEF with unselected cells and selected cells of a substantially lower number would argue for an important role for the selected cell population in the effects on cardiac function.

The mechanisms by which BMC therapy may improve cardiac function are still debated and not entirely clear. Whereas initial experimental studies had suggested a rapid transdifferentiation of BMCs (c-kit⁺, lineage⁻) into cardiomyocytes after cardiac injection post-MI,⁸ probably inspired by the concept of a high stem cell plasticity of adult stem cells, later experimental studies using genetic techniques to follow bone marrow cell fate reported that transdifferentiation of BMCs into cardiomyocytes did not explain the observed effects of BMCs on LV function,⁹ and suggested that BMCs act rather by paracrine mechanisms to improve cardiac function, such as by stimulation of capillary growth, prevention of cardiomyocyte apoptosis or stimulation of resident cardiac stem cells.^{10,11} In fact, inhibition of endogenous mobilization of stem cells from bone marrow after experimental MI augmented myocardial damage after MI and resulted in an impaired capillary growth in the infarct border zone.¹¹ The debate of the concept of stem cell plasticity, i.e. whether adult stem cells in addition to pluripotent stem cells can transdifferentiate into non-organ-specific cell types, is not unique to the cardiovascular field. Similarly, several groups had observed that adult BMCs repaired damaged liver tissue, which was initially suggested to result from transdifferentiation into liver cells, but later was reported to be a consequence of cell fusion with liver cells.¹² Cell fusion has also been suggested to explain in part the discrepant findings with respect to the transdifferentiation potential of BMCs into cardiomyocytes.¹³ Whether strategies to enhance cardiomyogenic differentiation of adult stem/progenitor cells, i.e. by activation of cardiogenic Wnt pathways¹⁴ or by small molecules,¹⁵ or whether induction of pluripotency¹⁶ will be required to enhance cardiomyogenesis efficiently remains one of the important future challenges.

While the initially perceived rapid chance for a complete cardiac repair by stem/progenitor cell therapy after MI has generated high expectations, now the potential of this therapy needs to be carefully developed by addressing important remaining questions, including the optimal cell types and pre-conditioning, the timing and dosing of cells to be used, how to augment the functional

repair capacity of transplanted cells, how to optimize their homing and engraftment in the heart, and how to select the patients that may benefit most from this therapy. An important focus of present basic and clinical studies is therefore directed towards optimizing the outcome and effect of stem/progenitor cell-based therapies, such as by improving stem/progenitor cell repair capacity and the process of cardiac cell homing. Notably, the vascular and pro-angiogenic repair capacity of autologous stem/progenitor cells is reduced by cardiovascular risk factors, such as diabetes,¹⁷ and by ageing, probably representing an important potential target for optimization of cell-based therapy. A reduced nitric oxide (NO) production by both circulating and bone marrow-derived stem/progenitor cells has been suggested to be critical for their reduced *in vivo* repair capacity.^{17,18} Augmented expression of endothelial NO synthase by gene transfer into endothelial progenitor cells prior to cardiac transplantation is currently being explored in the clinical ENACT-AMI trial as a strategy to augment cell repair capacity. Furthermore, several strategies are examined to improve homing and engraftment of mobilized stem/progenitor cells,¹⁹ i.e. the SITAGRAMI trial. Moreover, the timing and dosing of cell transplantation may be relevant for the effect of BMC therapy after MI, which is currently being examined in the SWISS-AMI and BOOST-2 trials.

Whereas the present clinical studies of BMC therapy have largely examined the effect on LVEF, i.e. a surrogate endpoint, ultimately the validation of cardiac cell therapy for clinical use will depend on the demonstration of a benefit with regard to clinical outcomes, similar to reperfusion therapy. In this respect, besides optimizing the conditions of cell therapy, selection of the patients who may benefit most from this therapy, i.e. based on LVEF and other parameters, will probably be an important issue to examine adequately the clinical potential of this novel therapeutic concept.

Conflict of interest: none declared.

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